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The US Food and Drug Administration's Perspective on the New Antidepressant Vortioxetine

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ABSTRACT

Objective: This article summarizes the US Food and Drug Administration's (FDA's) review of the New Drug Application for vortioxetine, especially the clinical efficacy and safety data. It emphasizes the issues that were important to the FDA's approval decision, particularly the difference in the effective dose in domestic and foreign studies, and notes several new labeling features, specifically, description of time course of treatment response and detailed sexual dysfunction evaluation.

Data Sources: The data sources were the original raw data sets for all clinical trials included in the development program for vortioxetine, as well as the sponsor's original analyses of these data. Data were available from 51 human trials involving vortioxetine, and included a total of 7,666 healthy volunteers and patients with a diagnosis of major depressive disorder (MDD) or generalized anxiety disorder who were exposed to at least 1 dose of vortioxetine for a total of 2,743 patient-years.

Results: Vortioxetine was effective in treating MDD in the United States at a dose of 20 mg/d. The recommended starting dose is 10 mg once daily without regard to food, with increase to 20 mg/d if the 10 mg/d dose is tolerated. For patients who do not tolerate 20 mg/d, 10 mg/d can be used and 5-mg/d dose can be considered. Vortioxetine can be discontinued abruptly, but it is recommended that doses of 15 mg/d or 20 mg/d be reduced to 10 mg/d for 1 week prior to full discontinuation to avoid potential withdrawal symptoms. Although the non-US maintenance study showed that maintenance doses of 5 to 10 mg/d were effective, a clinical judgment needs to be made to decide the maintenance dose in the United States. The applicant has agreed to conduct a US maintenance dose-response study covering the US-approved dose range. Vortioxetine's adverse event profile is similar to that of other selective serotonin reuptake inhibitors (SSRIs). Nausea is the most common adverse event and is dose dependent. No dose adjustment is needed based on age, gender, or the presence of renal or mild to moderate hepatic impairment. The maximum recommended dose is 10 mg/d in known cytochrome P450 2D6 poor metabolizers.

Conclusions: Vortioxetine is a new treatment for MDD, and its adverse event profile is similar to that of other SSRIs.

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The US Food and Drug Administration (FDA) approved vortioxetine, a serotonergic antidepressant, for the treatment of major depressive disorder (MDD) on September 30, 2013. This article summarizes the FDA's review of the New Drug Application (NDA) for vortioxetine, including the clinical efficacy and safety data collected from 51 human trials. It does not attempt to review the literature on vortioxetine; rather, it discusses the data that were important to the FDA's approval decision, differences in the effective doses in domestic and foreign studies, and several new features in the vortioxetine label compared to other antidepressants. The primary source documents for this article are the FDA's reviews and memoranda for the vortioxetine NDA, and these can be accessed at the FDA's website.[1] Where the controlled clinical trials have been published, we included available references,[2–8] although FDA review is based on the detailed data provided, not the published reports.

PHARMACOKINETIC PROFILE OF VORTIOXETINE

Vortioxetine exhibits dose-proportional pharmacokinetics with an absolute bioavailability of 75%. The time of maximum concentration (t_{max}) after dosing is between 7 and 11 hours. There is no identified food effect. The half-life of vortioxetine is approximately 66 hours, and vortioxetine concentration at steady state is approximately 5 times that observed after a single dose. Vortioxetine has no active metabolites.

Hepatic impairment (mild to moderate) and renal impairment (mild to end stage) do not appear to affect the clearance of vortioxetine and call for no dose adjustment. Patients with severe hepatic impairment have not yet been studied.

Vortioxetine is extensively metabolized through oxidation via multiple cytochrome P450 (CYP) enzymes, primarily CYP2D6, followed by subsequent glucuronic acid conjugation. CYP2D6 poor metabolizers have approximately twice the vortioxetine plasma concentration of extensive metabolizers. Therefore, the dose should be reduced to a maximum of 10 mg/d when vortioxetine is coadministered with a potent CYP2D6 inhibitor, such as bupropion. Vortioxetine doses should be increased up to 3-fold when vortioxetine is coadministered with a strong CYP inducer, such as rifampin.

THE EFFICACY AND SAFETY TRIALS

Ten short-term, placebo-controlled clinical trials (including 1 in elderly patients) and 1 maintenance (recurrence prevention) trial were conducted with vortioxetine in adults with a primary diagnosis of major depressive episode with MDD according to *DSM-IV-TR* criteria. Among the 10 short-term clinical trials, 6

were positive, ie, at least 1 dose was statistically significantly superior to the placebo in the treatment of MDD symptoms. The long-term maintenance study was also positive, with patients on vortioxetine treatment experiencing a statistically significantly longer time to recurrence of depression than patients taking placebo. These 7 positive studies were the basis for the FDA's approval of vortioxetine for the treatment of MDD. Of the remaining 4 studies, 3 were negative and 1 was considered a failed study. A negative trial was defined as one not showing superiority of vortioxetine to placebo on the primary efficacy measure at any dose. One study was considered a failed study because assay sensitivity was not established—the active control (duloxetine 60 mg, an FDA-approved antidepressant) failed to show a statistically significant effect compared to placebo.

Clinical Points

- Vortioxetine is a new antidepressant approved by the US Food and Drug Administration for the treatment of major depressive disorder.
- Besides the selective inhibition of serotonin reuptake, vortioxetine has pharmacologic activity at several other serotonin receptors. The possible contribution of these activities to the drug's antidepressant effect, however, is unknown.
- Substantial regional difference in efficacy was found between the US and non-US regions, with higher doses needed for effectiveness in the United States.
- Vortioxetine's safety profile is similar to that of other selective serotonin reuptake inhibitors.

Short-Term, Placebo-Controlled Studies

The 10 short-term trials were multicenter, randomized, double-blind, parallel group, placebo-controlled fixed-dose trials of 6 or 8 weeks' duration in adults (aged 18 to ≤ 75 years and, in the elderly study, ≥ 64 years) with MDD. Eligible patients were required to have a baseline Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 22, ≥ 26, or ≥ 30 in different studies. In the study in elderly patients, a score ≥ 24 on the Mini-Mental State Examination was required to exclude subjects with dementia.

The study populations across the 9 short-term studies (not including the study in the elderly) were similar with regard to disease characteristics and demographics, with a few exceptions noted below. Overall, the mean age of the subjects in the studies ranged between 42 and 47 years; 34% were male, and 66% were female. There were differences in racial distribution across studies, reflecting the fact that the studies were conducted in various geographical regions. Most subjects (79%) were white, 18% were black, and 1% were Asian. In the 5 studies conducted exclusively in the United States, the proportion of black subjects ranged from 21% to 28%, while in 3 of the 4 non-US studies, the proportion of Asian subjects ranged from 7% to 21%. In the elderly study, the mean age of subjects was 71 years and almost all (95%) were white.

The primary efficacy end points in the short-term studies were the change from baseline on either MADRS or 24-item Hamilton Depression Rating Scale (HDRS-24) total score. Patients were assessed at baseline and either weekly or every 2 weeks during the studies. The primary efficacy analysis on the full analysis set (all randomized patients who took at least 1 dose of study drug and who had at least 1 valid postbaseline measurement of the primary efficacy variable) used the mixed model for repeated measure in 5 studies, and an analysis of covariance with missing data imputed by the last observation carried forward in the other 5 studies.

Vortioxetine was developed for the treatment of MDD initially in the United States, Europe, Australia, Asia, and South Africa at doses up to 10 mg (1, 2.5, 5, and 10 mg) (Table 1; studies 1, 2, 6, 7, 9, and 10), with the 5- and 10-mg doses consistently showing effectiveness globally. The consistent failure of the 5-mg dose to show an effect in the United States (studies 9 and 10) led to further evaluation of higher doses (10, 15, and 20 mg) in the United States (studies 4, 5, and 8). An active reference, venlafaxine or duloxetine at doses of 225 mg and 60 mg, respectively, was included in 6 studies to assess assay sensitivity of the study. The failure of the 5-mg dose to show an effect in the US studies significantly influenced the FDA's dosing recommendations.

The efficacy of vortioxetine for the treatment of MDD was demonstrated in 6 short-term placebo-controlled studies, including the study in the elderly. In these studies, at least 1 dose of vortioxetine was significantly ($P < .05$) superior to placebo on the primary efficacy measure, either MADRS or HDRS-24, at the end of 6 or 8 weeks. The baseline MADRS or HDRS-24 total scores for these short-term studies ranged from 29 to 34. The higher doses were more effective, based on the primary efficacy measures in most studies, even though the differences between doses were generally not statistically significant. The 5-mg dose failed to show an effect in 2 large US studies. The efficacy results from the 10 short-term, placebo-controlled studies are summarized in Table 1.

Time Course of Treatment Response

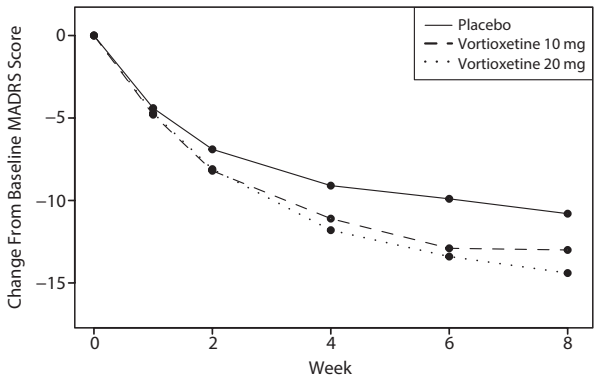
There has been great interest in examining when the efficacy of an antidepressant can be first identified during the course of treatment of acute depression, a matter of particular concern here given the relatively long half-life (about 3 days) of vortioxetine. We believe that describing the time of onset of treatment effect provides important information for health care providers and patients. Such information has been included in the product labeling of many FDA-approved drugs, but this is the first time it has been included in labeling of a psychiatric product. In the short-term placebo-controlled studies, the efficacy of vortioxetine became evident around week 2 and increased in subsequent weeks, with the full antidepressant effect generally observed by the fourth to sixth week. Figure 1 depicts the time course of response in a US study based on the primary efficacy measure (MADRS) (study 316 in Table 1).

Table 1. Primary Efficacy Results of Short-Term Controlled Studies

Study, Region	End Point (inclusion)	Drug Dose Groups	Treatment Effect (drug-placebo)	*P* Value (unadjusted)
1. (11492A) Europe, Asia, Australia, Canada	MADRS (≥ 30) Total n = 425	Vortioxetine 5 mg	−5.9	< .001
		Vortioxetine 10 mg	−5.7	< .001
		Venlafaxine 225 mg	−6.4	< .001
		Placebo	…	…
2. (305) Europe, Asia, Australia, South Africa	HDRS-24 (≥ 26) Total n = 419	Vortioxetine 5 mg	−4.1	< .001
		Vortioxetine 10 mg	−4.9	< .001
		Placebo	…	…
3. (13267A) Europe, South Africa	MADRS (≥ 26) Total n = 608	Vortioxetine 15 mg	−5.5	< .001
		Vortioxetine 20 mg	−7.1	< .001
		Duloxetine 60 mg	−9.5	< .001
		Placebo	…	…
4. (315) United States	MADRS (≥ 26) Total n = 591	Vortioxetine 15 mg	−1.5	.224
		Vortioxetine 20 mg	−2.8	.023
		Duloxetine 60 mg	−4.1	< .001
		Placebo	…	…
5. (316) United States	MADRS (≥ 26) Total n = 457	Vortioxetine 10 mg	−2.2	.058
		Vortioxetine 20 mg	−3.6	.002
		Placebo	…	…
6. (12541) (elderly) Europe, Canada, United States	HDRS-24 (≥ 26) Total n = 453	Vortioxetine 5 mg	−3.3	< .001
		Duloxetine 60 mg	−5.5	< .001
		Placebo	…	…
7. (11984A) Europe, Canada, Asia, Australia	MADRS (≥ 26) Total n = 600	Vortioxetine 5 mg	−1.7	.132
		Vortioxetine 10 mg	−1.5	.185
		Duloxetine 60 mg	−2.0	.074
		Placebo	…	…
8. (317) United States	MADRS (≥ 26) Total n = 434	Vortioxetine 10 mg	−0.8	.597
		Vortioxetine 15 mg	−0.5	.745
		Placebo	…	…
9. (303) United States	HDRS-24 (≥ 30) Total n = 578	Vortioxetine 5 mg	−0.7	.407
		Placebo	…	…
10. (304) United States	HDRS-24 (≥ 22) Total n = 451	Vortioxetine 5 mg	−0.6	.577
		Duloxetine 60 mg	−3.0	.005
		Placebo	…	…

Abbreviations: HDRS-24 = 24-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 1. Change From Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score by Study Visit (week) in Study 316



Maintenance Study

The maintenance study was a randomized withdrawal trial with a 12-week open-label, flexible-dose lead-in period followed by a randomized, double-blind, placebo-controlled fixed-dose period of 24 to 64 weeks. Six hundred thirty-nine patients meeting *DSM-IV-TR* criteria for MDD received flexible doses of vortioxetine, 5 mg/d or 10 mg/d, during an initial 12-week open-label treatment phase. The dose of vortioxetine was fixed during weeks 8 to 12. While receiving treatment, 396 patients who went into *remission* , defined as MADRS total score ≤ 10 at both weeks 10 and 12 after open-label treatment, were randomly assigned to continuation of the final fixed dose of vortioxetine (about 75% of patients were taking 10 mg/d) or to placebo for 24 to 64 weeks.

The primary efficacy end point was the time to recurrence of a major depressive episode during the first 24 weeks of the double-blind period. Recurrence of a depressive episode was defined as a MADRS total score ≥ 22 or lack of efficacy as judged by the investigator. Patients taking vortioxetine experienced a statistically significantly longer time to recurrence of depressive episodes than did patients on placebo (hazard ratio of drug to placebo: 0.50, $P < .01$). The overall proportion of subjects who relapsed was lower in the vortioxetine group (13%) than in the placebo group (26%). The Kaplan-Meier curve for time to relapse is shown in Figure 2.

Safety Findings for Vortioxetine

Overall, 7,666 adult healthy volunteers and patients with a diagnosis of MDD or generalized anxiety disorder (GAD) (aged 18 to 88 years) were exposed to at least 1 dose

Figure 2. Kaplan-Meier Estimates of Proportion of Patients With Recurrence

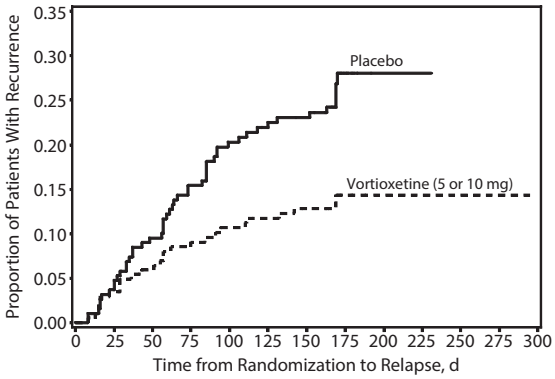


Table 2. Adverse Events Experienced by ≥ 5% Subjects and at Least Twice the Placebo Rate in Vortioxetine Treatment Groups by Preferred Term in the Pooled, Short-Term Trials in Major Depressive Disorder

		Vortioxetine, %				Duloxetine,
Preferred Term	Placebo (n = 1,621), %	5 mg (n = 1,013)	10 mg (n = 699)	15 mg (n = 449)	20 mg (n = 455)	60 mg (n = 753), %
Patients with any adverse events	62	66	67	70	73	77
Nausea	9	21	26	32	32	36
Vomiting	1	3	5	7	6	4
Constipation	3	4	5	6	6	10

of vortioxetine for a total of 2,743 patient-years in all clinical trials of MDD and GAD. Ten 6- or 8-week placebo-controlled MDD trials included 2,616 patients exposed to vortioxetine at doses ranging from 5 mg to 20 mg once daily, as well as 1,621 patients given placebo.

Death, Other Serious Adverse Events, and Adverse Dropouts

There were 6 deaths reported in the NDA, all of which occurred in vortioxetine treatment groups in the completed phase 2 and 3 clinical trials. The causes of death were reported as cancers (2 cases), suicide (1 case), morphine toxicity (1 case), road traffic accident (1 case), and accidental fall (1 case). The FDA reviewers did not consider the deaths drug related.

Overall, 134 patients experienced a nonfatal serious adverse event in the MDD and GAD program. The proportions of patients experiencing nonfatal serious adverse events were similar for vortioxetine, placebo, and active control, duloxetine 60 mg/d. Many of the serious adverse events were psychiatric in nature and probably represented worsening of the underling condition being treated.

In pooled 6- to 8-week placebo-controlled studies, the rates of patients who discontinued treatment with vortioxetine 5 mg/d, 10 mg/d, 15 mg/d, and 20 mg/d because of an adverse reaction were 5%, 6%, 8%, and 8%, respectively, compared to 4% of placebo-treated patients. Nausea was the most common adverse reaction reported as a reason for discontinuation.

Common and Nonserious Adverse Events

Three adverse events were considered to be common and drug related (ie, occurring at a rate of at least 5% with vortioxetine and at least twice the placebo rate) on the basis of pooled MDD short-term trials and included nausea, vomiting, and constipation. The rates for these 3 adverse events are shown in Table 2.

Nausea

Nausea was the most common adverse event, and its frequency was dose related. It was usually mild or moderate in intensity, and the median duration was 2 weeks. Nausea was reported more in female than male patients. Nausea most commonly occurred in the first week of vortioxetine treatment, with 15%–20% of patients experiencing nausea after 1 to 2 days of treatment. Approximately 10% of patients taking vortioxetine 10 mg/d to 20 mg/d had nausea at the end of the 6- or 8-week placebo-controlled trials versus 5% for duloxetine.

Adverse Reactions Following Abrupt Discontinuation of Vortioxetine Treatment

Discontinuation symptoms have been reported with many antidepressants. These adverse reactions were prospectively evaluated in patients taking vortioxetine 10 mg/d, 15 mg/d, and 20 mg/d using the Discontinuation-Emergent Signs and Symptoms Scale in 3 clinical trials. Although vortioxetine was not expected to have significant adverse reactions following abrupt treatment discontinuation because of its

long half-life (66 hours), about 5% patients who took higher doses (15 mg/d or 20 mg/d) experienced discontinuation symptoms such as headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week of abrupt discontinuation. Given these findings, vortioxetine labeling indicates that the drug can be discontinued abruptly, but a dose reduction to 10 mg/d for 1 week prior to full discontinuation is recommended if possible.

MAJOR ISSUES IN APPROVAL DECISION

Mechanism of Action

As is the case for all antidepressants, the mechanism of vortioxetine's antidepressant effect is not known with certainty. However, for vortioxetine, the mechanism of action is thought to be related to enhancement of serotonergic activity in the central nervous system through inhibition of the reuptake of serotonin. In in vitro studies[1] using cloned human transporters, vortioxetine potently and selectively inhibited the reuptake of serotonin (half maximal inhibitory concentration [IC_{50}] = 5.4 nM) by binding with high affinity to the serotonin transporter (K_i = 1.6 nM), but showed much lower affinity at the norepinephrine (K_i = 113 nM) or dopamine (K_i > 1,000 nM) transporters.

Vortioxetine clearly has other pharmacologic activities. In vitro and animal data indicate that vortioxetine may have activity at 5 serotonin (5-HT) receptors: 5-HT_3, 5-HT_{1A}, 5-HT_7, 5-HT_{1D}, and 5-HT_{1B}.* However, the net effect of these potential activities on serotonergic transmission and their possible contribution to the drug's antidepressant effect or other clinical effects have not been documented or adequately explored. Despite the increased binding to various targets, there was no evidence of an advantage in clinical efficacy or safety of vortioxetine treatment compared with either venlafaxine extended release or duloxetine, which served as active controls in the clinical studies. The overall efficacy and safety profiles of vortioxetine are similar to those of other SSRIs. There are possible study designs that could reveal possible clinical differences, such as studies in patients who do not respond to or do not tolerate SSRIs, but no such studies have been attempted. Where there were comparisons with venlafaxine and duloxetine, no differences favoring vortioxetine were seen (studies 11492A, 13267A, 315, 12541, 11984A, and 304). Thus, there is no evidence of a clinically meaningful benefit of the activity at any or all of the additional 5 serotonin receptor targets.

Nevertheless, pharmacologic activity of vortioxetine at each of those 5 serotonin receptors (5-HT_3, 5-HT_{1A}, 5-HT_7, 5-HT_{1D}, and 5-HT_{1B}) was included in the Clinical Pharmacology section of labeling under Mechanism of Action and/or Pharmacodynamics, with a qualifying statement that "... contribution of these activities to vortioxetine's antidepressant effect has not been established."[1] Two of these receptors—5-HT_3 and 5-HT_{1A}—were included under Mechanism of Action based on published clinical studies[9–19] that suggest 5-HT_3 receptor antagonists and 5-HT_{1A} receptor agonists may have an effect in the treatment of depression. However, at the time vortioxetine was approved, no such published clinical studies supported an antidepressant effect for the other 3 receptors—5-HT_7, 5-HT_{1D}, and 5-HT_{1B}. Moreover, the evidence that these receptors might contribute to the mechanism of action of vortioxetine was considered weak, as it was based on data from only in vitro human and rat receptor binding studies, *ex vivo* and in vivo occupancy studies in rat brain, and behavioral and electrophysiological studies in rat. Finally, because vortioxetine's activity as an inhibitor of the serotonin reuptake transporter appears adequate to account for its antidepressant activity, there was no reason to invoke additional hypothetical mechanisms for its antidepressant activity. We therefore included activity at 5-HT_7, 5-HT_{1D}, and 5-HT_{1B} receptors only under Pharmacodynamics and did not add these activities to Mechanism of Action in the vortioxetine label.[1]

Dose Determination and Regional Difference

Overall, the effectiveness of vortioxetine in the treatment of MDD was demonstrated for daily doses of 5 mg, 10 mg, 15 mg, and 20 mg, and the higher doses were generally somewhat more effective in each trial (see Table 1). However, in the United States, the dose of 5 mg failed to show efficacy in any trial, and only the highest dose, 20 mg, demonstrated superiority to the placebo in the clinical trials. Moreover, the effect sizes for any dose were also consistently smaller in the US trials (see Table 1). Interestingly, in the elderly study (number 12541), a multiregional investigation that included about one-third US patients (n = 171/448), a much smaller effect size was observed in the US region not only with vortioxetine treatment (5 mg) (−0.7 vs −4.9 on the HDRS-24 in US and non-US regions, respectively) but also with the active control, duloxetine 60 mg (2.8 vs 7.1 in HDRS-24 in US and non-US regions, respectively). The effect size of duloxetine 60 mg observed in the US region was less than half of that observed in the non-US regions. Both the applicant and FDA analyzed data on demographic information, disease severity, placebo effects, and body mass index by region and found no single factor that explained the regional differences.

In the United States, only vortioxetine 20 mg showed consistent efficacy, although there was some evidence that the 10-mg dose was effective. In US study 316, 10 mg of vortioxetine was statistically significantly better than placebo on change from baseline in MADRS total score up to week 6 (−3.0 points, $P < .01$). Although not statistically significantly different at week 8, the difference from placebo was −2.2 points ($P = .058$). After considering all the data obtained, labeling,[1] therefore, recommends starting with vortioxetine 10 mg and then increasing the dose to 20 mg if 10 mg is tolerated. For some patients who do not tolerate the higher dose, a dose of 5 mg may be considered.

*Based on in vitro data using recombinant human receptors, vortioxetine is a potent 5-HT_3 receptor antagonist (half maximal inhibitory concentration [IC_{50}] = 3.5 nM), moderate 5-HT_{1A} receptor agonist (IC_{50} = 199 nM), weak 5-HT_7 receptor antagonist (IC_{50} = 450 nM), moderate 5-HT_{1D} receptor antagonist (IC_{50} = 25 nM), and weak to moderate 5-HT_{1B} receptor partial agonist (IC_{50} = 120–460 nM).

Table 3. ASEX Incidence in ≥ 2% of Treatment-Emergent Sexual Dysfunction[a]

	Vortioxetine				Duloxetine	
Patients	5 mg (n = 65:67)[b]	10 mg (n = 94:86)[b]	15 mg (n = 57:67)[b]	20 mg (n = 67:59)[b]	60 mg (n = 109:99)[b]	Placebo (n = 135:162)[b]
Female, %	22	23	33	34	28	20
Male, %	16	20	19	29	26	14

[a]Incidence based on number of subjects with sexual dysfunction during the study/number of subjects without sexual dysfunction at baseline. *Sexual dysfunction* was defined as a subject scoring any of the following on the ASEX at 2 consecutive visits during the study: (1) total score ≥ 19, (2) any single item ≥ 5, or (3) 3 or more items each with a score ≥ 4.
[b]Sample size for each dose group is the number of patients (female:male) without sexual dysfunction.
Abbreviation: ASEX = Arizona Sexual Experience Scale.

In an effort to understand the impact of foreign data on psychiatric drug approvals, the FDA's Division of Psychiatry Products conducted exploratory analyses[20] of efficacy data from randomized, placebo-controlled, multicenter trials submitted in NDAs for antidepressants over a 25-year period (1983–2008) and examined differences between North American and non–North American regions in baseline demographic and disease characteristics, placebo response, and treatment effect. This analysis showed that there was no difference in the overall treatment effect (ie, the drug-placebo difference), and the overall trial success rate was higher in North American than in non–North American regions (58% vs 33%).[20] The regional difference observed in the NDA for vortioxetine is, thus, different from the findings seen previously by the Division of Psychiatry Products at the FDA. The reasons underlying this discrepancy are unknown.

Sexual Dysfunction

Sexual dysfunction, such as decreased libido, abnormal orgasm, delayed ejaculation, and erectile dysfunction, is a well-recognized adverse reaction of SSRI and serotonin-norepinephrine reuptake inhibitor antidepressants. In the vortioxetine development program, sexual dysfunction was assessed both by spontaneous reports of sexually related adverse events and through use of the Arizona Sexual Experience Scale (ASEX). It is well known that voluntary reports of sexually related adverse events understate the sexual dysfunction of antidepressants, as is reflected in most antidepressant labeling. In the MDD short-term pool, spontaneously reported adverse events related to sexual dysfunction were infrequent (< 5% in vortioxetine and < 2% in placebo), and there was no significant difference between the drug and placebo treatments. The results of the ASEX analysis used in 7 short-term, controlled clinical trials (see Table 1; studies 3, 4, 5, 7, 8, and 10; and 1 trial in patients with GAD, study 308), in contrast, showed that treatment-emergent sexual dysfunction was numerically more frequent in vortioxetine groups than placebo and appeared to be dose related. For both male and female patients without sexual dysfunction at baseline, the treatment-emergent sexual dysfunction with vortioxetine, which occurred at a rate of at least 2% and at 2 consecutive postbaseline visits, was higher than that with placebo but similar to the active control, duloxetine 60 mg/d (Table 3).

POSTMARKETING COMMITMENTS AND REQUIREMENTS

As noted, the maintenance study used daily doses of 5 mg and 10 mg, doses with less than full effectiveness in acute studies in the United States. As effective reduction in recurrent depression is critically important, we asked the applicant to commit to conducting a fixed-dose, placebo-controlled maintenance study in the United States covering the dose range of 5 mg/d to 20 mg/d. Under the Pediatric Research Equity Act,[21] all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to assess safety and effectiveness of the treatment in pediatric patients. The FDA required the applicant to conduct postmarketing pediatric studies in children and adolescents aged 7 to 17 years with MDD. We also required a study to characterize the major metabolites of vortioxetine and a study of vortioxetine pharmacokinetics in patients with severe impairment of hepatic function.

CLINICAL SUMMARY

Vortioxetine was approved for the treatment of MDD by the FDA in September 2013. It is available in 5-, 10-, 15-, and 20-mg immediate-release tablets. The recommended starting dose is 10 mg once daily taken without regard to meals. The dose should be increased to 20 mg/d if tolerated. For patients who do not tolerate 20 mg/d, 10 mg/d can be used, and a 5-mg/d dose can be considered. Vortioxetine can be discontinued abruptly, but it is recommended that doses of 15 mg/d or 20 mg/d be reduced to 10 mg/d for 1 week prior to full discontinuation to avoid potential withdrawal symptoms. Although the non-US maintenance study (11984A) showed that maintenance doses of 5 to 10 mg/d were effective, it is standard practice with antidepressants to continue treatment of patients who have improved during short-term treatment with the dose they responded to. Because only the dose of 20 mg/d showed clear efficacy in the United States, clinical judgment should be applied to determine the maintenance dose.

Vortioxetine's profile of adverse events is similar to that of other SSRIs. Nausea is the most common adverse event and is dose-dependent. Consistent with the FDA's practice of including class effects in labeling, vortioxetine has a warning in its label for serious adverse events observed with other serotonergic antidepressants.

Pharmacokinetic findings suggest that dose adjustment is not needed based on age, gender, renal impairment, or mild to moderate hepatic impairment. No overall differences in safety or effectiveness were observed between younger and elderly (≥ 65 years) patients. Cytochrome P450 2D6 is the primary enzyme catalyzing the metabolism of vortioxetine. The maximum recommended dose is 10 mg/d in known CYP2D6 poor metabolizers.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), duloxetine (Cymbalta and others), morphine (Avinza, Kadian, and others), rifampin (Rifadin, Rimactane, and others), venlafaxine (Effexor and others), vortioxetine (Brintellix).

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Additional information: The primary source documents for this article are the FDA's reviews and memoranda for the vortioxetine New Drug Application, and these can be accessed at the FDA's website (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204447Orig1s000TOC.cfm).

REFERENCES

1. US Food and Drug Administration. Drug Approval Package. Brintellix (Vortioxetine) tablets. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204447Orig1s000TOC.cfm. Updated October 30, 2013. Accessed August 18, 2014.
2. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5mg and 5mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin*. 2013;29(3):217–226.
3. Jain R, Mahableshwarkar AR, Jacobsen PL, et al. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *Int J Neuropsychopharmacol*. 2013;16(2):313–321.
4. Henigsberg N, Mahableshwarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry*. 2012;73(7):953–959.
5. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol*. 2012;27(4):215–223.
6. Boulenger JP, Loft H, Florea I. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. *J Psychopharmacol*. 2012;26(11):1408–1416.
7. Baldwin DS, Loft H, Dragheim M. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). *Eur Neuropsychopharmacol*. 2012;22(7):482–491.
8. Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2012;15(5):589–600.
9. Faris PL, Eckert ED, Kim SW, et al. Evidence for a vagal pathophysiology for bulimia nervosa and the accompanying depressive symptoms. *J Affect Disord*. 2006;92(1):79–90.
10. Haus U, Varga B, Stratz T, et al. Oral treatment of fibromyalgia with tropisetron given over 28 days: influence on functional and vegetative symptoms, psychometric parameters and pain. *Scand J Rheumatol Suppl*. 2000;113(Suppl 29):55–58.
11. Hewlett WA, Schmid SP, Salomon RM. Pilot trial of ondansetron in the treatment of 8 patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 2003;64(9):1025–1030.
12. Johnson BA, Ait-Daoud N, Ma JZ, et al. Ondansetron reduces mood disturbance among biologically predisposed, alcohol-dependent individuals. *Alcohol Clin Exp Res*. 2003;27(11):1773–1779.
13. Piche T, Vanbiervliet G, Cherikh F, et al. Effect of ondansetron, a 5-HT3 receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study. *Gut*. 2005;54(8):1169–1173.
14. Ansseau M, Pitchot W, Moreno AG, et al. Pilot study of flesinoxan, a 5-HT1A agonist, in major depression: effects on sleep REM latency and body temperature. *Hum Psychopharmacol*. 1993;8(4):279–283.
15. Bielski RJ, Cunningham L, Horrigan JP, et al. Gepirone extended-release in the treatment of adult outpatients with major depressive disorder: a double-blind, randomized, placebo-controlled, parallel-group study. *J Clin Psychiatry*. 2008;69(4):571–577.
16. Feiger AD, Heiser JF, Shrivastava RK, et al. Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder. *J Clin Psychiatry*. 2003;64(3):243–249.
17. Grof P, Joffe R, Kennedy S, et al. An open study of oral flesinoxan, a 5-HT1A receptor agonist, in treatment-resistant depression. *Int Clin Psychopharmacol*. 1993;8(3):167–172.
18. Keller MB, Ruwe FJ, Janssens CJ, et al. Relapse prevention with gepirone ER in outpatients with major depression. *J Clin Psychopharmacol*. 2005;25(1):79–84.
19. Trivedi MH, Fava M, Wisniewski SR, et al; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1243–1252.
20. Khin NA, Chen YF, Yang Y, et al. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. *J Clin Psychiatry*. 2011;72(4):464–472.
21. Pediatric Product Development. Pediatric Research Equity Act (PREA). US Food and Drug Administration web site. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm. Updated June 25, 2014. Accessed October 20, 2014.